

We claim:

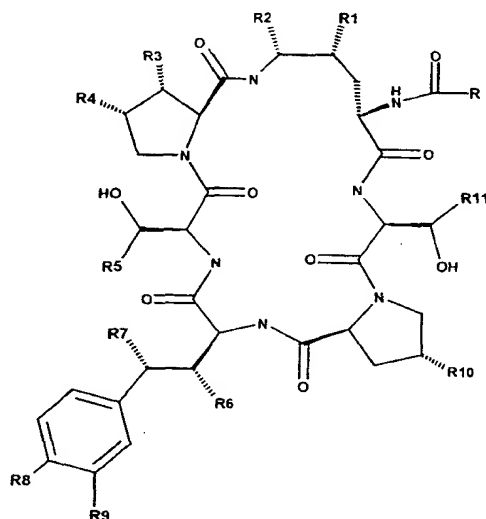
1. A process for preparing an oral pharmaceutical formulation comprising the steps of:

(i) mixing an echinocandin compound or echinocandin/carbohydrate complex and at least one carbohydrate in a solvent or mixture of solvents to form a pharmaceutical solution;

(ii) spraying said solution onto a layer of fluidized granular diluent or carrier; and

(iii) removing the excess of said solvent or solvents to form granules.

2. The process of Claim 1 wherein said echinocandin compound or echinocandin of said echinocandin/carbohydrate complex is represented by the following structure:



wherein:

R is an alkyl group, an alkenyl group, an alkynyl group, an aryl group, heteroaryl group, or combinations thereof;

R₁, R₂, R₃, R₆, R₇, and R₁₀ are independently hydroxy or hydrogen;

R₄ is hydrogen, methyl or -CH₂C(O)NH₂;

R₅ and R₁₁ are independently methyl or hydrogen;

R_8 is -OH, -OPO₃H₂, -OPO₃HCH₃, -OPO₂HCH₃, or -OSO₃H;

R_9 is -H, -OH, or -OSO₃H; and

pharmaceutically acceptable salts thereof.

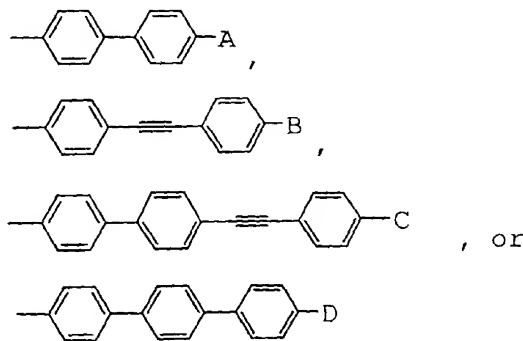
3. The process of Claim 2 wherein

5 R_4 , R_5 and R_{11} are each methyl;

R_2 and R_7 are independently hydrogen or hydroxy; R_1 , R_3 , R_6 and R_{10} are each hydroxy;

R_8 is -OH, -OPO₃HCH₃, or -OPO₂HCH₃;

10 R is linoleoyl, palmitoyl, stearoyl, myristoyl, 12-methylmyristoyl, 10,12-dimethylmyristoyl, or a group having the general structure:



where A, B, C and D are independently hydrogen, C₁-C₁₂ alkyl, C₂-C₁₂ alkynyl,

C₁-C₁₂ alkoxy, C₁-C₁₂ alkylthio, halo, or

15 -O-(CH₂)_m-[O-(CH₂)_n]_p-O-(C₁-C₁₂ alkyl), or

-O-(CH₂)_q-X-E; m is 2, 3 or 4;

n is 2, 3 or 4; p is 0 or 1; q is 2, 3 or 4;

X is pyrrolidino, piperidino or piperazino;

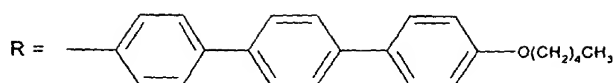
E is hydrogen, C₁-C₁₂ alkyl, C₃-C₁₂ cycloalkyl, benzyl or C₃-C₁₂

20 cycloalkylmethyl.

4. The process of Claim 3 wherein

R_2 and R_7 are each hydroxy;

R_8 is hydroxy; and

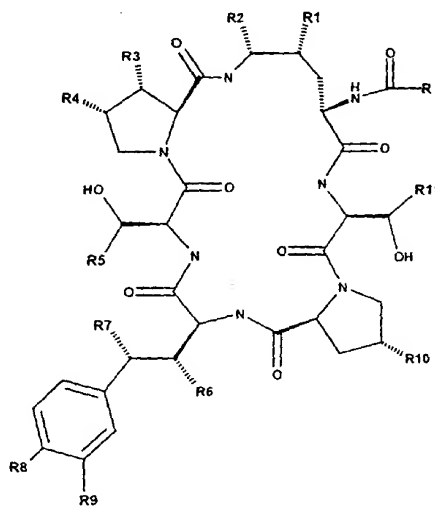


5. The process of Claim 1 wherein said at least one carbohydrate is selected from the group consisting of adonitol, arabinose, arabitol, ascorbic acid, chitin, D-cellubiose, 2-deoxy-D-ribose, dulcitol, (S)-(+)-erythrulose, fructose, fucose, galactose, glucose, inositol, lactose, lactulose, lyxose, maltitol, maltose, maltotriose, mannitol, mannose, melezitose, melibiose, microcrystalline cellulose, palatinose, pentaerythritol, raffinose, rhamnose, ribose, sorbitol, sorbose, starch, sucrose, trehalose, xylitol, xylose and hydrates thereof.
6. The process of Claim 1 wherein said at least one carbohydrate is selected from the group consisting of L-arabinose, D-arabitol, L-arabitol, 2-deoxy-D-ribose, (S)-(+)-erythrulose, D-fructose, D-(+)-fucose, L-fucose, D-galactose, β -D-glucose, D-lyxose, L-lyxose, D-maltose, maltotriose, melezitose, palatinose, D-raffinose, D-sorbitol, D-trehalose, xylitol, L-xylose and hydrates thereof.
7. The process of Claim 4 wherein said mixture of solvents is acetone and water.
8. The process of Claim 7 wherein said acetone is present in an amount from 50% to 70% based on volume relative to said water.
9. The process of Claim 1 wherein said granular diluent or carrier is selected from the group consisting of adonitol, arabinose, arabitol, ascorbic acid, chitin, D-cellubiose, 2-deoxy-D-ribose, dulcitol, (S)-(+)-erythrulose, fructose, fucose, galactose, glucose, inositol, lactose, lactulose, lyxose, maltitol, maltose, maltotriose, mannitol, mannose, melezitose, melibiose, microcrystalline cellulose, palatinose, pentaerythritol, raffinose, rhamnose, ribose, sorbitol, sorbose, starch, sucrose, trehalose, xylitol, xylose, polyethylene glycols, hydroxypropyl methylcelluloses, hydroxypropyl methylcellulose phthalates, dextrans and hydrates thereof.
10. The process of Claim 1 wherein said granular diluent or carrier is a carbohydrate selected from the group consisting of fructose, glucose, lactose, lactulose, maltitol, maltose, maltotriose, mannitol, mannose, microcrystalline

cellulose, hydroxypropyl methylcellulose, hydroxypropyl methylcellulose phthalate, dextrates, dextrin, sorbitol, sorbose, starch, sucrose, trehalose, xylitol, xylose and hydrates thereof.

11. The process of Claim 1 wherein said granular diluent or carrier is selected
5 from the group consisting of mannitol, lactose, maltose and hydrates thereof.
12. The process of Claim 1 wherein said echinocandin compound is present in said granules in an amount from about 5% to 25% by weight.
13. The process of Claim 1 wherein said echinocandin compound is present in said granules in an amount from about 7% to 20% by weight.
- 10 14. The process of Claim 1 wherein said echinocandin compound is present in said granules in an amount from about 12% to 16% by weight.
15. The process of Claim 1 wherein said carbohydrate is present in said granules in an amount from about 5% to 25% by weight.
- 15 16. The process of Claim 1 wherein said carbohydrate is present in said granules in an amount from about 7% to 20% by weight.
17. The process of Claim 1 wherein said carbohydrate is present in said granules in an amount from about 12% to 16% by weight.
18. The process of Claim 1 wherein said carrier or diluent is present in said granules in an amount from about 50% to 90% by weight.
- 20 19. The process of Claim 1 wherein said carrier or diluent is present in said granules in an amount from about 60% to 80% by weight.
20. The process of Claim 1 wherein said carrier or diluent is present in said granules in an amount from about 65% to 75% by weight.
21. The process of Claim 1 wherein said pharmaceutical solution further
25 comprises excipients selected from the group consisting of surfactants, flavorings, colorants, processing aids, and combinations thereof.

22. An oral pharmaceutical formulation prepared by the process of Claim 1.
23. A medicament comprising an oral pharmaceutical formulation of Claim 22.
24. The medicament of Claim 23 wherein said medicament is in the form of a chewable tablet or sachet.
- 5 25. A method for treating a fungal infection comprising administering an effective amount of an oral pharmaceutical formulation of Claim 22 to a host in need thereof.
26. A process for preparing an oral pharmaceutical formulation comprising the steps of:
- (i) mixing an echinocandin compound or echinocandin/carbohydrate complex,
- 10 at least one carbohydrate and a soluble granulating agent in a solvent or mixture of solvents to form a pharmaceutical solution;
- (ii) spraying said solution onto a layer of fluidized non-granular diluent or carrier; and
- (iii) removing the excess of said solvent or solvents to form granules.
- 15 27. The process of Claim 26 wherein said echinocandin compound or echinocandin of said echinocandin/carbohydrate complex is represented by the following structure:



wherein:

R is an alkyl group, an alkenyl group, an alkynyl group, an aryl group, heteroaryl group, or combinations thereof;

R_1 , R_2 , R_3 , R_6 , R_7 , and R_{10} are independently hydroxy or hydrogen;

5 R_4 is hydrogen, methyl or $-\text{CH}_2\text{C}(\text{O})\text{NH}_2$;

R_5 and R_{11} are independently methyl or hydrogen;

R_8 is $-\text{OH}$, $-\text{OPO}_3\text{H}_2$, $-\text{OPO}_3\text{HCH}_3$, $-\text{OPO}_2\text{HCH}_3$, or $-\text{OSO}_3\text{H}$;

R_9 is $-\text{H}$, $-\text{OH}$, or $-\text{OSO}_3\text{H}$; and

pharmaceutically acceptable salts thereof.

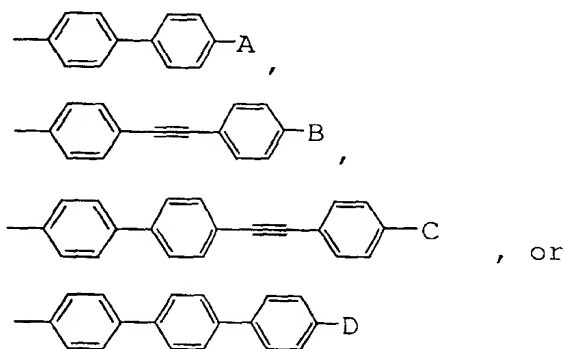
10 28. The process of Claim 27 wherein

R_4 , R_5 and R_{11} are each methyl;

R_2 and R_7 are independently hydrogen or hydroxy; R_1 , R_3 , R_6 and R_{10} are each hydroxy;

R_8 is $-\text{OH}$, $-\text{OPO}_3\text{HCH}_3$, or $-\text{OPO}_2\text{HCH}_3$;

15 R is linoleoyl, palmitoyl, stearoyl, myristoyl, 12-methylmyristoyl, 10,12-dimethylmyristoyl, or a group having the general structure:



where A, B, C and D are independently hydrogen, C_1 - C_{12} alkyl, C_2 - C_{12} alkynyl, C_1 - C_{12} alkoxy, C_1 - C_{12} alkylthio, halo, or

20 $-\text{O}-(\text{CH}_2)_m-[\text{O}-(\text{CH}_2)_n]_p-\text{O}-(\text{C}_1-\text{C}_{12} \text{ alkyl})$ or

$-\text{O}-(\text{CH}_2)_q-\text{X}-\text{E}$; m is 2, 3 or 4;

n is 2, 3 or 4; p is 0 or 1; q is 2, 3 or 4;

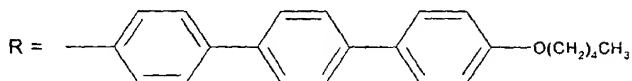
X is pyrrolidino, piperidino or piperazino;

E is hydrogen, C₁-C₁₂ alkyl, C₃-C₁₂ cycloalkyl, benzyl or C₃-C₁₂ cycloalkylmethyl.

29. The process of Claim 28 wherein

R₂ and R₇ are each hydroxy;

5 R₈ is hydroxy; and



30. The process of Claim 26 wherein said at least one carbohydrate is selected from the group consisting of adonitol, arabinose, arabitol, ascorbic acid, chitin, D-cellulbiose, 2-deoxy-D-ribose, dulcitol, (S)-(+)-erythrulose, fructose, fucose, galactose, 10 glucose, inositol, lactose, lactulose, lyxose, maltitol, maltose, maltotriose, mannitol, mannose, melezitose, melibiose, microcrystalline cellulose, palatinose, pentaerythritol, raffinose, rhamnose, ribose, sorbitol, sorbose, starch, sucrose, trehalose, xylitol, xylose and hydrates thereof.

15 31. The process of Claim 26 wherein said at least one carbohydrate is selected from the group consisting of L-arabinose, D-arabitol, L-arabitol, 2-deoxy-D-ribose, (S)-(+)-erythrulose, D-fructose, D-(+)-fucose, L-fucose, D-galactose, β-D-glucose, D-lyxose, L-lyxose, D-maltose, maltotriose, melezitose, palatinose, D-raffinose, D-sorbitol, D-trehalose, xylitol, L-xylose and hydrates thereof.

20 32. The process of Claim 29 wherein said mixture of solvents is acetone and water.

33. The process of Claim 32 wherein said acetone is present in an amount from 50% to 70% based on volume relative to said water.

25 34. The process of Claim 26 wherein said non-granular diluent or carrier is selected from the group consisting of adonitol, arabinose, arabitol, ascorbic acid, chitin, D-cellubiose, 2-deoxy-D-ribose, dulcitol, (S)-(+)-erythrulose, fructose, fucose, galactose, glucose, inositol, lactose, lactulose, lyxose, maltitol, maltose, maltotriose, mannitol, mannose, melezitose, melioiose, microcrystalline cellulose, palatinose,

pentaerythritol, raffinose, rhamnose, ribose, sorbitol, sorbose, starch, sucrose, trehalose, xylitol, xylose, polyethylene glycols, hydroxypropyl methylcelluloses, hydroxypropyl methylcellulose phthalates, dextrates and hydrates thereof.

35. The process of Claim 26 wherein said non-granular diluent or carrier is a carbohydrate selected from the group consisting of fructose, glucose, lactose, lactulose, maltitol, maltose, maltotriose, mannitol, mannose, microcrystalline cellulose, hydroxypropyl methylcellulose, hydroxypropyl methylcellulose phthalate, dextrates, dextrin, sorbitol, sorbose, starch, sucrose, trehalose, xylitol, xylose and hydrates thereof.

36. The process of Claim 26 wherein said granular diluent or carrier is selected from the group consisting of mannitol, lactose, maltose and hydrates thereof.

37. The process of Claim 26 wherein said echinocandin compound is present in said granules in an amount from about 5% to 25% by weight.

38. The process of Claim 26 wherein said echinocandin compound is present in said granules in an amount from about 7% to 20% by weight.

39. The process of Claim 26 wherein said echinocandin compound is present in said granules in an amount from about 12% to 16% by weight.

40. The process of Claim 26 wherein said carbohydrate is present in said granules in an amount from about 5% to 25% by weight.

41. The process of Claim 26 wherein said carbohydrate is present in said granules in an amount from about 7% to 20% by weight.

42. The process of Claim 26 wherein said carbohydrate is present in said granules in an amount from about 12% to 16% by weight.

43. The process of Claim 26 wherein said carrier or diluent is present in said granules in an amount from about 50% to 90% by weight.

44. The process of Claim 26 wherein said carrier or diluent is present in said granules in an amount from about 60% to 80% by weight.

45. The process of Claim 26 wherein said carrier or diluent is present in said granules in an amount from about 65% to 75% by weight.

46. The process of Claim 26 wherein said granulating agent is polyvinylpyrrolidone.

5 47. The process of Claim 26 wherein said pharmaceutical solution further comprises excipients selected from the group consisting of surfactants, flavorings, colorants, processing aids, and combinations thereof.

48. An oral pharmaceutical formulation prepared by the process of Claim 26.

49. A medicament comprising an oral pharmaceutical formulation of Claim 48.

10 50. The medicament of Claim 49 wherein said medicament is in the form of a chewable tablet or sachet.

51. A method for treating a fungal infection comprising administering an effective amount of an oral pharmaceutical formulation of Claim 48 to a host in need thereof.